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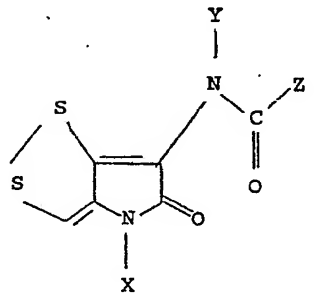
(54) Processes for making fungicidal dithiolopyrrolones

(57) Processes for making compounds of formula:



(I)

wherein X, Y and Z which may be the same or different are an optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or hydrogen atom and when Y is methyl X is not a hydrogen atom, are described.

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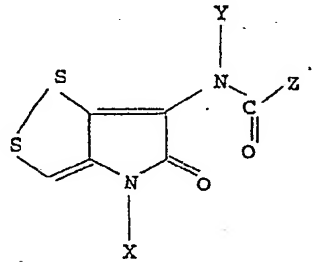
SPECIFICATION

Processes for making heterocyclic compounds

This invention relates to processes for making heterocyclic compounds having biological activity and especially useful as fungicides.

The invention provides processes for making compounds having the general formula (I):



(I)

wherein X, Y and Z, which may be the same or different, are optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or a hydrogen atom and when Y is methyl X is not a hydrogen atom, the processes comprising any of the reaction sequences 1 to 4 hereinafter set forth; or any part of, or combination of, these reaction sequences; or any individual step thereof.

Alkyl groups can be in the form of straight or branched chains, and preferably contain 1 to 6 carbon atoms.

Several compounds having the general formula (I), wherein Y is a hydrogen atom and X is either a hydrogen atom or a methyl group, which are naturally occurring compounds, some with fungicidal activity, have been described in the literature. Examples of these compounds are thiolutin (I, X=Z=CH_3, Y=H) (see The Merck Index, ninth edition, 1976, p 1206; and references therein), holomycin (I,X=Y=H, Z=CH_3) (see The Merck Index, ninth edition, 1976, p. 620; and references therein) and the Xenorhabdin antibiotics (see CSIRO (1984) Australian Patent Applic. No. 127365). Compounds (I) derived from naturally occurring thiolutin, wherein X is a methyl group and Y is a hydrogen atom are the subject of Brit. Pat. (1956) Pub. No. 753,331. Also compound (I), wherein Y is a methyl group and both X and Z are hydrogen atoms is a naturally occurring compound with antibiotic activity (see B. Jensen, *J. Antibiotics*, 1969, *22*, 231).

Preferred alkyl groups for X, Y and Z from 1 to 6, especially 1 to 4, carbon atoms. Preferred cycloalkyl groups are cyclopropyl cyclobutyl, cyclopentyl, and cyclohexyl. The alkyl moiety in aralkyl groups preferably contains from 1 to 4 carbon atoms.

Preferred alkenyl groups contain from 3 to 6 carbon atoms and include allyl.

The compounds may contain chiral centres. Such compoundsare generally obtained in the form of racemic mixtures. However, these and other mixtures can be separated into theindividual isomers by methods known inthe art.

Examples of suitable substituent groups for X, Y and Z when they represent aralkyl, aralkenyl or aryl, especially benzyl or phenyl, are halogen, haloalkyl, alkyl, alkoxy (especially containing 1 to 4 carbon atoms), optionally substituted phenyl and optionally substituted phenoxy.

Suitably the aryl, especially phenyl group, is unsubstituted or substituted with 1, 2 or 3 ring substituents, which may be the same or different, as defined above. Examples of X, Y and Z are phenyl, 2-, 3- or 4-chlorophenyl, 2,4- or 2,6-dichlorophenyl, 2,4- or 2,6-difluorophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2-, 3- or 4-methyl-phenyl, 2-, 3- or 4-ethylphenyl, 2-, 3- or 4-trifluoro-methylphenyl, 4-phenylphenyl (4-biphenylyl), 2-chloro-4-methoxyphenyl), 2-fluoro-4-methoxyphenyl, 2-chloro-4-methylphenyl, 2-fluoro-4-methylphenyl, 4-isopropylphenyl, 2-methyl-4-chlorophenyl or 2-methyl-4-fluorophenyl.

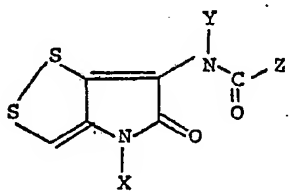
When X, Y and Z is alkyl it can be a straight or branched chain alkyl group having 1 to 6, eg. 1 to 4 carbon atoms; examples are methyl, ethyl, propyl (*n*- or *iso*-propyl) and butyl (*n*-, *sec*-, *iso*- or *t*-butyl); when X, Y and Z is alkenyl it can be allyl.

The salts can be salts with inorganic or organic acids eg. hydrochloric, nitric, sulphuric, acetic, 4-toluenesulphonic or oxalic acid.

Several total syntheses of compounds of type (I), wherein Y is a hydrogen atom and X is either a hydrogen atom or a methyl group have been described in the literature (Schmidt and Geiger, *Annaler*, 1963, *664*, 168; G.Büchi and B.Lukas, J.Amer.Chem.Soc., 1964, *86*, 5654; K.Hagio and N.Yoneda, *Chem.Pharm.Bull.*, 1974, *47*, 1484). The partial synthesis of compounds of type (I), wherein Y is a hydrogen atom and X is a methyl group, from naturally occurring thiolutin (I, X=Z=CH_3; Y=H) has also been described (Brit.Pat.No. 753,331). The processes described in this invention have several advantages over these existing methods. The starting materials used are relatively cheap and readily available. Furthermore, the synthetic sequences described herein are shorter and give better overall yields of final products even when carried out on a large scale. In addition, the processes are sufficiently versatile to permit the variation of the substituent groups X, Y and Z

as defined above. Examples of the compounds which can be prepared by the processes of the present invention are shown in Table I. These conform to formula I and in each instance the groups X, Y and Z are as shown in the table "Ph" stands for C_6H_5 ie. for phenyl.

TABLE 1



Compound numbers	X	Y	Z	Melting point (°C)
1	CH_3	CH_3	CF_3	214 (dec)
2	CH_3	CH_3	$CO_2C_2H_5$	85
3	CH_3	CH_3	CH_3	216
4	CH_3	CH_3	CH^t Ph CH_2 CH	203-205
5	$PhCH_2$-	CH_3	CH^t Ph CH_2 CH	86-89
6	$PhCH_2$-	CH_3	H	gum
7	$PhCH_2$-	H	CH_3	186
8	$PhCH_2$-	H	CF_3	214
9	$PhCH_2$-	H	H	207 (dec)
10	$PhCH_2$-	H	$CO_2C_2H_5$	115
11	$PhCH_2$-	H	CO_2CH_3	172
12	$PHCH_2$-	H	CH^t Ph CH_2 CH	225
13	$PhCH_2$-	H	CH_2OCH_3	96-98
14	$PhCH_2$-	H	$(CH_2)_4CH_3$	142-144
15	$PhCH_2$-	H	$C(CH_3)_3$	Oil
16	Ph	H	CH_3	287
17	C_2H_5	H	CH_3	223-226 (dec)
18	C_2H_5	H	CF_3	204-205
19	C_2H_5	H	H	219-223
20	CH_2 CH_2 CH	H	CH_3 CH_3 C Cl CH_2	228-231
21	CH_2 CH_2 CH	H		154-156
22	p-CH_3O-C_6H_4-	H	CH_3	
23	*i*-C_3H_7	H	CH_3	
24	*i*-C_3h_7	CH_3	H	
25	*n*-C_4H_9	H	CF_3	
26	*n*-C_3H_7	H	$COOC_2H_5$	
27	*i*-C_3H_7	H	$COOCH_3$	
28	CH_3	Ph	$COOC_2H_5$	
29	CH_3	Ph	CF_3	

The compounds of the invention having the general formula (I) can be prepared by the steps shown in *Schemes 1-4*. Throughout *Schemes 1-4* the terms X, Y and Z are as defined above; R^1, R^2 and R^3, which may be the same or different, are alkyl or aralkyl groups; R^1 and R^2 may be joined to form part of a ring; and A and B are halogen atoms or good leaving groups, which may be the same or different.

Thus, compounds of general formula (I) can be prepared by treatment of compounds of general formula (II) with an oxidising agent such as iodine, (see, for example, Schmidt and Geiger, *Annalen*, 1963, *664*, 168) or air, (see, for example, K.Hagio and N.Yoneda, *Chem. Pharm. Bull.*, 1974, *47*, 1484) in a convenient solvent such as dichloromethane (see Scheme 1).

Compounds of general formula (II), which may exist as mixtures of geometric isomers, can be prepared from compounds of general formula (II) by treatment with an alkali metal, such as lithium (when $R^1=R^2=$benzyl) in a convenient solvent, such as liquid ammonia, (see, for example, G.Büchi and G.Lukas, *J.Amer.Chem.Soc.*, 1964, *36*, 5654) or by treatment with transition metal satls, such as mercury (II) acetate or copper (II) acetate (when $R^1=R^2=$^{t}Butyl; or $R^1=R^2=$alkyidene, for example methylene or isopropylidene) in a suitable solvent, such as trifluoroacetic acid, followed by treatment with hydrogen sulphide in a suitable

solvent, such as dimethylformamide, (see, for example, O.Nishimura, C.Kitada and M.Fujino, *Chem.Pharm. Bull.*, 1978, *26*, 1576).

Compounds of general formula (III), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (IV) by treatment with an acylating agent, such as acetylchloride, in the presence or absence of an acid-binding agent (such as triethylamine) in a suitable solvent, such as dichloromethane or chloroform or tetrahydrofuran, and at a convenient temperature (such as 0 to 80°C).

Compounds of general formula (IV), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (V) by treatment with a salt of an amine YNH_2, such as ammonium acetate or anilinium acetate, with or without a convenient solvent (such as acetic acid), and at a convenient temperature (such as 80 to 160°C).

Compounds of general formula (V), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of type (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) by treatment with oxalyl chloride or bromide in the presence of an acid-binding agent (such as triethylamine) in a suitable solvent (such as dichloromethane or chloroform) and at a convenient temperature (such as −78°C to 25°C) (Scheme 2).

Alternatively, compounds of the general formula (V) can be prepared from esters of general formula (VII) by treatment with a suitable base (such as sodium hydride, lithium di-isopropylamide or lithium hexamethyldisilazide) in a suitable solvent (such as tetrahydrofuran or diethyl ether) and at a convenient temperature (−78°C to 25°C).

In addition, compounds of the general formula (V) can be prepared from compounds of general formula (IV) by hydrolysis in a suitable solvent (such as water or ethanol) in the presence of a suitable catalyst (such as hydrochloric acid) (see, for example, K.Hagio and N.Yoneda, *Chem.Pharm.Bull*, 1974, *47*, 1484) (Scheme 1).

Esters of general formula (VII), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) by treatment with a suitable acylating agent, such as ethyl oxalyl chloride or methyloxalyl chloride in the presence or absence of an acid-binding agent (such as triethylamine) in a suitable solvent such as dichloromethane or chloroform) and at a convenient temperature (such as 0°C).

Compounds of general formula (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) can be prepared from ketones of general formula VII by treatment with an amine $X\text{-}NH_2$ in the presence of a dehydrating agent (such as titanium tetrachloride) in a suitable solvent (such as diethyl ether) and at a convenient temperature (−78°C to 25°C).

Ketones of general formula (VII) can be prepared from ketones of general formula VIII by treatment with a thiol of general formula R^1SH or R^2SH in the presence of a base (such as sodium hydride, sodium methoxide) in a suitable solvent (such as diglyme, ethanol or tetrahydrofuran) and at a convenient temperature (such as −25°C to 50°C).

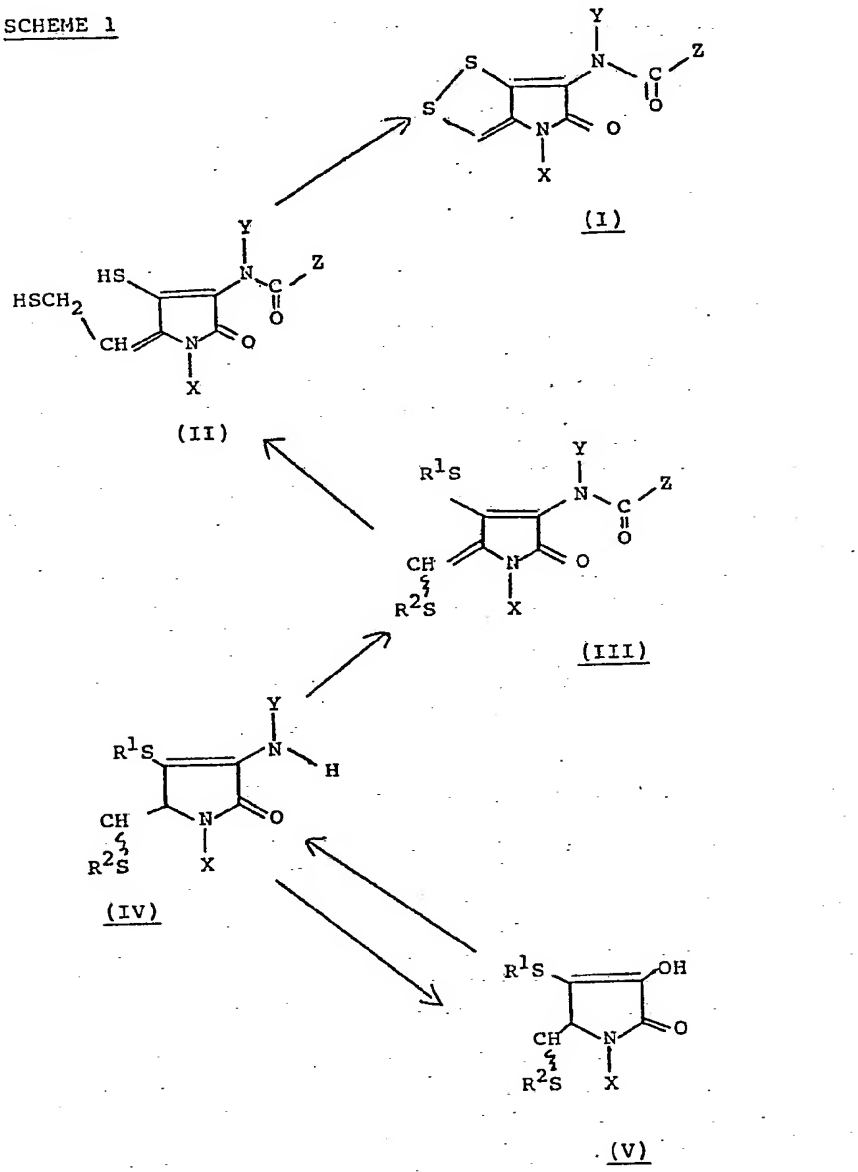
Alternatively ketones of general formula (VII) can be prepared from β-keto-esters of general formula (IX) by treatment with a salt (such as lithium chloride) in a suitable solvent (such as dimethylsulphoxide) and at a convenient temperature (such as 110°C to 189°C) (see, for example, A.P.Krapcho, J.F.Weimaster, J.M.Eldridge, E.G.E.Jahngen, Jr., A.J.Lovey, W.P. Stephens, *J.Org. Chem*, 1978, *43*, 138) or by decarboxylation of β-keto-acids of general formula (IX), using standard methods as set out in the chemical literature (see, for example, H.O.House, *Modern Synthetic Methods*, 2nd edition, p.511).

β-Keto-acids of general formula (IX) can be prepared from β-keto-esters of general formula (X) using standard methods as set out in the chemical literature (see, for example, H.O.House, *Modern Synthetic Methods*, 2nd edition, P.511).

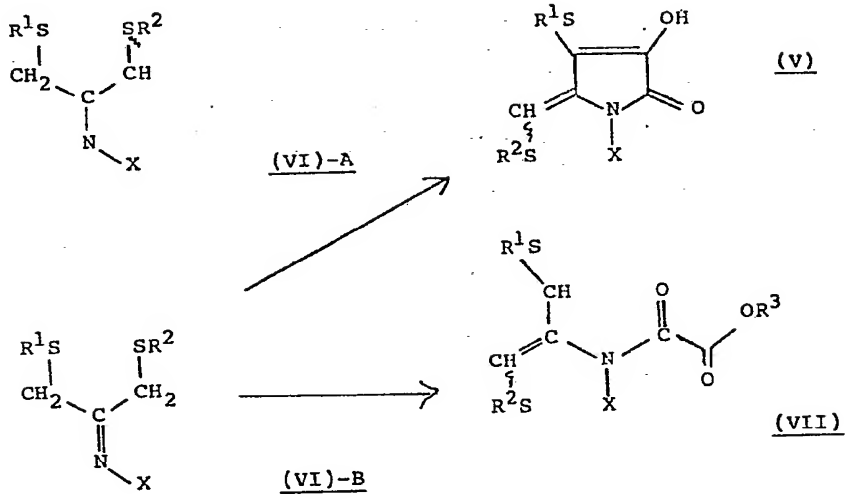
β-Keto-esters of general formula (X) can be prepared from esters of general formula (XI) or (XII) by treatment with a base (such as sodium hydride) in a suitable solvent (such as tetrahydrofuran) and at a suitable temperature (such as 0°C to 100°C) (Scheme 3).

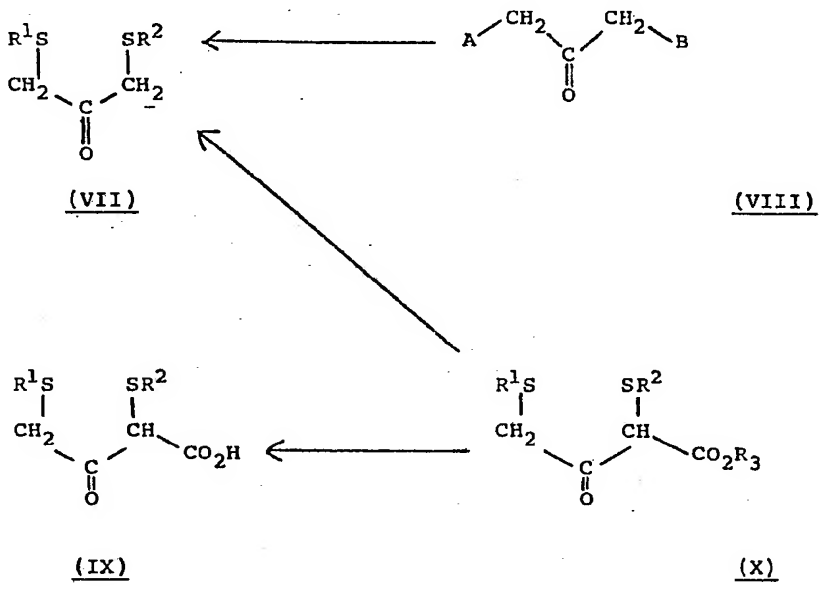
Compounds of general formula IV, where X=Y, which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (V), where X is an aryl substituent (such as a phenyl group) on treatment with a salt of an amine $Y\text{-}NH_2$, such as ammonium acetate, with or without a convenient solvent (such as acetic acid), and at a convenient temperature (such as 80°C to 160°C) (Scheme 4).

SCHEME 1



SCHEME 2

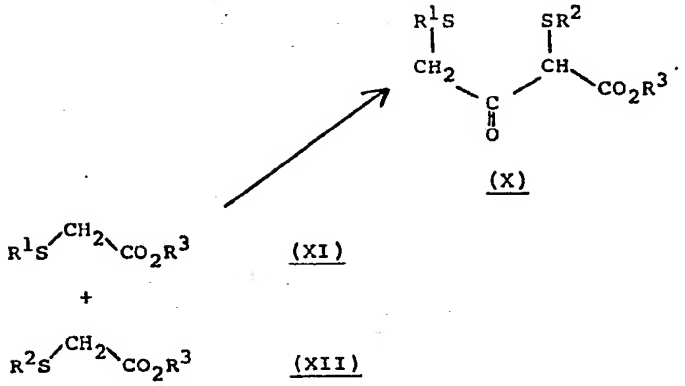




(VII) (VIII)

(IX) (X)

SCHEME 3



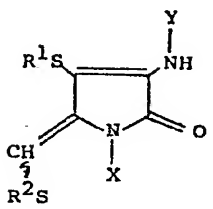
(X)

(XI)

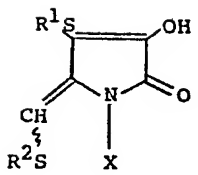
+

(XII)

SCHEME 4



(IV) X=Y



(V) X=aryl

The following Examples illustrate the invention; the temperatures are given in degrees Centigrade (°C).

Example 1

This example illustrates the preparation of 5-(methoxyacetylamino)-4-benzyl-1,2-dithiolo[4,3-b]pyrrol-5(4H)-one (Compound No. 13 of Table I).

To a solution of sodium methoxide in dry methanol (formed by the addition of sodium (10,58g) to dry methanol (200ml)) was slowly added a solution of *t*-butylmercaptan (41,5g) in dry methanol (50ml). The resultant solution was cooled to 0°C and a solution of 1,3-dichloro-acetone (29.21g) in dry methanol (50ml) was added over a period of 1 hour. The resultant mixture was stirred for a further 16 hours at room temperature and then partitioned between dichloromethane and dilute sodium hydroxide solution. The organic phase was dried over magnesium sulphate, filtered and evaporated to give a liquid. Distillation at 96°C/1mbar afforded 1,3-di(*t*-butylthio) acetone (VII, $R^1=R^2=t$-Bu-see Scheme 2) (26.42g, 49%). In an alternative procedure, t-butylmercaptan (500g) was added drop-wise over 6½ hours to a slurry of sodium hydride (80% dispersion in oil, 163g) in dry diglyme (2.22 litres) under an atmosphere of nitrogen. The reaction was exothermic and the rate of addition was set to hold the temperature below 40°C. A white suspension formed which thickened as the reaction progressed. After stirring overnight, the suspension was diluted with a further 400mls of diglyme and cooled to 0-5°C. A solution of 1,3-dichloro-acetone in diglyme (710mls) was then added drop-wise over a period of 6 hours. The reaction mixture was allowed to warm up to room temperature over 1 hour and then methanol (50mls) was added to destroy excess sodium hydride. The resultant mixture was partitioned between water (4 litres) and toluene (3 litres). The aqueous layer was back-extracted with toluene (2 litres) and the combined organic layers were washed with water (2x3 litres), dried and concentrated *in vacuo* to afford 1,3-di(*t*-butylthio)acetone (VII, $R^1=R^2=t$-Bu – see Scheme 2) (570g, 88%) which could if desired be used in the next stage of the synthesis without further purification.

To a solution of 1,3-di(*t*-butylthio)acetone (25g) in sodium-dried diethyl ether (150ml) at room temperature was added a solution of benzylamine (29.8g) in sodium-dried diethyl ether (50ml). After 1 hour, titanium tetrachloride (10.1g) was added slowly and stirring was continued at room temperature for a further 3 hours. The resultant mixture was filtered through celite and the solvent removed *in vacuo* to afford the benzylimine of 1,3-di(*t*-butylthio) acetone (VI-B, X=Bz, $R^1=R^2=t$-Bu- see Scheme 2) as a brown oil (23.07g) which was used immediately in the next stage of the synthesis without further purification.

To a solution of oxalyl chloride (8.91g) in dry dichloromethane (300ml) at 50°C was added a solution containing the benzylimine of 1,3-di(*t*-butylthio)acetone (22.7g) and triethylamine (7.1g) in dry dichloromethane (600ml). The mixture was stirred for 2 hours, allowed to warm up to room temperature and then washed with water, sodium bicarbonate solution and saturated brine. The organic phase was dried over sodium sulphate, filtered and evaporated to give a brown oil. Trituration with petrol followed by chromatography of the residue on silica (eluent: dichloromethane-diethyl ether mixtures) afforded compound (V, X=Bz $R^1=R^2=t$-Bu - see Scheme 1) as a brown solid (14.8g, 56%, m.p. 158°C.

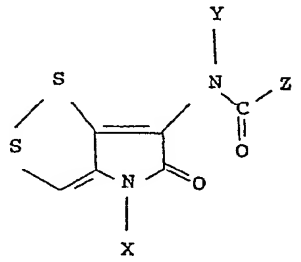
Compound (V, X=Bz,$R^1=R^2=t$-Bu - see Scheme 1) (1.4g) and ammonium acetate (2.86g) were ground together into a fine powder and then fused at *ca* 140°C for 2 hours. The mixture was allowed to cool and then taken up into dichloromethane. The organic phase was basified with sodium bicarbonate solution, washed with water and brine, and the dried over anhydrous magnesium sulphate. The resultant solution was filtered through a silica plug (eluent-diethylether) to afford, after evaporation, compound (IV, X=Bz, Y=H, $R^1=R^2=t$-Bu - Scheme 1) as a brown solid (1.27g 91%), m.p. 119-120°C.

To a solution of (IV; X=Bz, Y=H $R^1=R^2=t$-Bu - see Scheme 1) (1.0g) in sodium-dried tetrahydrofuran (50ml) was added methoxyacetyl chloride (0.57g). The resultant solution was stirred at room temperature for 16 hours. The tetrahydrofuran was evaporated off and replaced by dichloromethane. The resultant solution was washed with sodium bicarbonate solution and dried over anhydrous magnesium sulphate. Filtration through a silica plug (eluent-diethyl ether) gave compound (III, X=Bz, Y=H, $Z=CH_2OCH_3$, $R^1=R^2=t$-Bu - see Scheme 1) as an oil (0.87g, 73%), ($CDCl_3$) 1,37 (18H); 3.48 (3H,S); 4.04 (2HS); 5.22 (2H,S); 6.80 (1H,S); 7.25 (5H, n); 8.18 (1H,br.s).

To a solution of compound (II, X=Bz, Y=H, $Z=CH_2OCH_3$, $R^1=R^2=t$-Bu) (0.85g) in trifluoroacetic acid (20ml) was added mercury (II) acetate (0.60g). The resultant solution was stirred at room temperature for one hour and the trifluoracetic acid then removed by evaporaton *invacuo*. The solid residue was redissolved in *N*, *N*-dimethylformamide (20ml) and treated with hydrogen sulphide at room temperature for two hours. Nitrogen was then bubbled through the reaction mixture to remove traces of hydrogen sulphide and the black suspension was filtered through celite. A solution of iodine (0.48g) in chloroform (20ml) was added at room temperature and the solution stirred at room temperature for thirty minutes. The solvents were removed by evaporation *in vacuo*, and the residue was separated on silica (eluent diethyl ether) to afford 6-(methoxyacetylamino)-4-benzyl-1,2-dithiolo[4,3-b] pyrrol-5(4H)-one (Compound No. 13 of Table I) as a yellow solid. (408mg, 64%, m.pt. 96-98°C, ($CDCl_3$) 3.49 (3H,S); 4.02 (2H,S); 4.99 (2H,S); 6.48 (1H,S); 7.26 (5H, M); 8.50 (1H,br.s); m/e 334 M^+), 289, 275, 261, 241, 91, 45.

CLAIMS

1. Processes for making compounds having the general formula (I):



(I)

wherein X, Y and Z, which may be the same or different, are optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or a hydrogen atom and when Y is methyl X is not a hydrogen atom, the processes comprising any of the reaction sequencs 1 to 4 hereinafterset forth; or any part of, or combination of, these reaction sequences; or any individual step thereof.

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